337751

8EHQ-11-18426

Submission under TSCA Section 8(e)

August 25, 2011

TSCA Confidential Business Information Center (7407M)
EPA East - Room 6428 Attn: Section 8(e)
U.S. Environmental Protection Agency
1200 Pennsylvania Avenue, NW
Washington, DC 20460-0001

Contains Confidential Business Information

Re: n=1PMPA(N)

To Whom It May Concern:

By this letter, [ ] is notifying the U.S. Environmental Protection Agency ("EPA") under Section 8(e) the Toxic Substances Control Act ("TSCA") regarding a studies of the above-captioned substance for Prenatal Developmental Toxicity Study following Oral (Gavage) Administration in Hannover Wistar Rats and Reproduction/Developmental Toxicity Screening Test following Oral (Gavage) Administration in Wistar Rats. The test substance used in this study is subject to the TSCA Section 5(e) Order issued for [ ].

Study Title: Prenatal Developmental Toxicity Study following Oral (Gavage) Administration in Hannover Wistar Rats

Study objective and method: The objective of the study was to assess the effects of the test item on pregnant females and on the developing conceptuses and provide general information concerning the effects of prenatal exposure on the pregnant test animal and

on the developing organism; this included assessment of maternal effects as well as death, structural abnormalities, or altered growth in the foetus. One control and 3-treated groups of Hannover Wistar rats were treated daily by oral (gavage) administration between GD5 and GD19, where the day of mating (when the sperm-positive vaginal smear, and/or the vaginal plug was identified) was regarded as gestation day 0 (GD0).

Mated, assumed pregnant female Hannover Wistar rats were treated as follows:

Group no.	Group no./ Designation	Dose Level n=1PMPA(N) active ingredient (mg/kg/day)
1	Control	0
2	Low dose	10
3	Mid dose	50
4	High dose	200

Results: The no observed adverse effect level (NOAEL) for n=1PMPA(N) for reproductive toxicity was considered to be 50 mg active ingredient/kg bw/day in pregnant females due to the decrease in fertility and/or implantation in the highest dose (200 mg) group.

Study Title: Reproduction/Developmental Toxicity Screening Test following Oral (Gavage) Administration in Wistar Rats

Study objective and method: The purpose of this study was to obtain initial information on the possible effects of the test item on reproduction and development by repeated daily oral gavage administration to CRL:(WI)BR rats. As a screening test, it was intended to provide initial information on possible effects on male and female reproductive performance such as gonadal function, mating behaviour, conception,

pregnancy, parturition as well as on development of the F1 offspring from conception to day 4 post-partum associated with administration of repeated doses.

Twelve male and 12 female CRL:(WI)BR Wistar rats/group were treated as below:

Gr. No.	Group Designation	Dose Level n=1PMPA(N) active ingredient (mg/kg/day)
1	Control	0
2	Low Dose	1
3	Mid Dose	10
4	High Dose	100

Results: For developmental effects in the offspring, the NOAEL for n=1PMPA(N) was 10 mg/kg bw/day based on the fact that in the 100 mg/kg bw/day treatment group postnatal mortality was statistically higher than the control group. For reproductive effects in the adults, the NOAEL was considered to be the high dose, 100 mg/kg bw/day, because there were no significant differences between the control and the other dose groups with regard to reproductive ability, including mating, fertility and gestation indices.

Thank you for your attention to this matter.

Respectfully submitted,

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To Whom It May Concern:

By this letter, [ ] is notifying the U.S. Environmental Protection Agency ("EPA") under Section 8(e) the Toxic Substances Control Act ("TSCA") regarding a study of the above-captioned substance administered to rats by oral gavage for 13 weeks. The test substance used in this study is subject to the TSCA Section 5(e) Order issued for [ ].

In this study, four groups of male rats were dosed at 0 (control), 0.02, 0.1 and 0.5 milligrams per kilogram per day ("mg/kg") and four groups of female rats were dosed at 0 (control), 0.5, 5 and 50 mg/kg. In each species group, there were 10 animals in the low and middle dose groups and 15 animals in the control and high dose groups. Five animals in the control and high dose groups were retained after the completion of the 13 week dosing period for examination of the reversibility of any observed effects.

In the male rats, there were increases in liver weight and indications of liver toxicity in the middle and high dose groups. Blood chemistry evaluation showed increases in albumin, albumin/globulin ("A/G") ratio and total protein in these same dose groups. ALAT levels showed a increase in the high dose group. In the kidney at the middle and high dose, there was a increase in relative organ weight and indications of hypertrophy of the proximal tubular epithelium. In addition, hypertrophy in cortical cells of the adrenal glomerular zone was indicated in the high dose group.

In the female rats, there were indications of liver enlargement in the high dose group and hypertrophy of the liver in the middle and high dose groups. Blood chemistry indicated increases for albumin, A/G ratio and total protein in the high dose group. Hypertrophy of the proximal tubular epithelium of the kidney was observed in the high dose group.

Company Sanitized

Reversibility of the treatment-related changes was observed in the high dose groups after the recovery period, with the exception of liver toxicity in males. Under the conditions of the study, the No Observed Adverse Effect Level was considered to be 0.02 mg/kg for males and 0.5 mg/kg in females.

Thank you for your attention to this matter.

Respectfully submitted,

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By this letter, [ ] is notifying the U.S. Environmental Protection Agency ("EPA") under Section 8(e) the Toxic Substances Control Act ("TSCA") regarding a studies of the above-captioned substance for

- Mammalian Erythrocyte Micronucleus Test in Bone Marrow Cells of Mouse, - Micronucleus Test using Rats,
- *In vivo/in vitro* Unscheduled DNA Synthesis (UDS) Test Using Rat Livers,
- Chromosome Aberration Test in Cultured Mammalian Cells

The test substance used in this study is subject to the TSCA Section 5(e) Order issued for [ ].

Study Title: Mammalian Erythrocyte Micronucleus Test in Bone Marrow Cells of Mouse

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Study objective and method: The main objective of this study was to determine the chromosomal damage or damage to mitotic apparatus in a mammalian test in vivo. The basis of this assay is an increase in micronuclei in the polychromatic erythrocytes of treated animals versus controls.

This study followed the procedures indicated by the following internationally accepted guidelines and recommendations:

- Ninth Addendum to OECD Guidelines for Testing of Chemicals, Section 4, No. 474, "Mammalian Erythrocyte Micronucleus Test." adopted 21st July, 1997
- Commission Regulation (EC) No 440/2008 of 30 May 2008 laying down test methods pursuant to Regulation (EC) No 1907/2006 of the European Parliament and of the Council on the Registration, Evaluation, Authorisation and Restriction of Chemicals (REACH), B.12. MUTAGENICITY — IN VIVO MAMMALIAN ERYTHROCYTE MICRONUCLEUS TEST.
- EPA Health Effects Test Guidelines, OPPTS 870.5395 " Mammalian Erythrocyte Micronucleus Test " August-1998.

Results: Under the conditions of this assay the test substance did induce an increase in the number of micronucleated polychromatic erythrocytes at 24 or 48 hours after a single intraperitoneal injection at dose levels of 125 and 62.50 mg/kg body weight/day in CRL:NMRI BR mice.

Study Title: Micronucleus Test using Rats

Study objective and method: The test substance was assessed in an *in vivo* micronucleus test in male Crl:CD(SD) rats (8 weeks old at dosing) to examine its ability to induce micronucleated erythrocytes in the bone marrow as an index for assessing its genotoxic potential to induce chromosome aberration *in vivo*. (OECD GUIDELINE FOR THE TESTING OF CHEMICALS, "Mammalian Erythrocyte Micronucleus Test," No. 474 Adopted on 21st July 1997).

The animals (5 animals per group) received oral gavage administration of the negative control (water for injection), test substance (62.5, 125, 250 and 500 mg/kg) and positive

control (cyclophosphamide monohydrate, 20 mg/kg) twice at a 24-hour interval. Bone marrow cells were collected 24 hours after the final administration. Bone marrow cell specimens were prepared to determine the incidence of micronucleated immature erythrocytes (MNIMEs) and percentage of immature erythrocytes (IMEs).

Results: It was concluded that the test substance did not induce micronucleated erythrocytes in rat bone marrow under the conditions employed in this study, and that the test substance did not have a genotoxic potential to induce chromosome aberration *in vivo*.

Study Title: *In vivo/in vitro* Unscheduled DNA Synthesis (UDS) Test Using Rat Livers

Study Objective and Method: The test substance was tested in an unscheduled DNA synthesis (UDS) test using male Crl:CD(SD) rats (8 weeks old at dosing) to examine its ability to induce DNA damage *in vivo* in the liver. (OECD GUIDELINES FOR THE TESTING OF CHEMICALS, "Unscheduled DNA Synthesis (UDS) Test with Mammalian Liver Cells In Vivo" No. 486 Adopted on 21 July 1997).

The animals (3 animals per group) received oral gavage administration of the negative control (water for injection), test substance (60, 200, 600 and 2000 mg/kg) and positive control (dimethylnitrosamine and 2-acetylaminofluorene at 10 and 50 mg/kg, respectively). Hepatocytes were isolated from the livers of treated animals at 2 or 16 h after the administration by the collagenase perfusion method, and incubated in the presence of ^{3}H-thymidine. The incidences of UDS in the cultures were detected by autoradiography.

Results: Based on the results of this study, it was concluded that the test substance did not induce UDS in rat hepatocytes and that the test substance has no potential to induce DNA damage in the liver *in vivo* under the conditions employed in this study.

Study: Title Chromosome Aberration Test in Cultured Mammalian Cells

Study Objective and Method: To evaluate the clastogenic potential of the test substance in cultured mammalian (Chinese hamster lung CHL/IU) cells.

-Short term test: Cells were treated for 6 hours in the presence and absence of a metabolic activation system, rat liver S9 mix. Dosing without metabolic activation was 125, 250, 500 and 1000 μg/mL. Dosing with metabolic activation was 250, 500, 1000 and 1500 μg/mL.

-Continuous test: Cells were continuously treated for 24 hours without metabolic activation. The test substance was dissolved in physiological saline and administered to the test cells at doses of 31.3, 62.5, 125 and 250 μg/mL.

Results: Based on the criteria in the draft revised guidance of ICH (International Conference on Harmonization) S2(R1) on genotoxicity testing, the clastogenicity of the test substance was judged to be negative.

No significant increase in the frequency of aberrant metaphases was observed at any concentration in the short-term treatment without metabolic activation and in the continuous treatment.

An increase in the frequency of metaphases with chromosome aberrations was observed in the short-term treatment with metabolic activation at the highest concentration of 1500 μg/mL. At this concentration, however, a large reduction in the relative cell growth was observed simultaneously, which suggests that the detected chromosome aberrations were secondarily derived from severe cytotoxic damage induced by the test substance..

No significant increases in the frequency of polyploid metaphases were observed at any concentration of the test substance either with or without metabolic activation.

Under the conditions of this study the clastogenic potential of the test substance is equivocal in the presence of metabolic activation in Chinese hamster CHL/IU cells, but according to the draft revised guidance of ICH (International Conference on Harmonization) S2(R1) on genotoxicity testing, the clastogenicity of the test substance is judged negative

because the high dose in this study exceeded the recommended maximum exposure concentration of 1 mM or 0.5 mg/mL.

Thank you for your attention to this matter.

Respectfully submitted,

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